REMARKS

Applicants thank the Examiner for her review of the instant application, and acknowledge the withdrawal of the objections to the title, abstract, specification and Claims 1-13, and the withdrawal of the rejection of Claims 1-6, 9, 10 and 12-13 as being indefinite.

Claims 4 and 5 have been canceled. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application. Claim 12 has been amended to change the claim dependency from canceled Claim 4 to Claim 6. Claims 6, 9, 10, 14-15 have been amended to delete "the extracellular domain of the polypeptide" and recite "amino acids 23-223." Applicants maintain that the amendments add no new matter, and that support for the amendments can be found in the specification as filed, for example in Figure 46.

Claims 6-17 are presented for examination. For the reasons stated below, the rejections of the presently pending claims are respectfully traversed.

Priority

The PTO asserts that because the disclosure of PCT/US00/23328 is not enabling for the instant invention, the filing date of the present application, May 2, 2002, is considered the priority date. For the reasons of record, Applicants maintain that the present application is entitled to at least the priority date of August 24, 2000.

Rejection Under 35 U.S.C. §101

The PTO maintains its rejection of pending Claims 6-17 under 35 U.S.C. § 101 as lacking utility for the reasons set forth in the previous Office Action. Briefly stated, the PTO argues that because there is no correlation between gene amplification and mRNA levels, or between mRNA levels and protein levels, the reported differential expression of the PRO1138 mRNA does not provide utility for the claimed polypeptides.

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the PTO has not met its burden of providing evidence showing that one of ordinary skill

in the art would reasonably doubt the asserted utility. However even if the PTO has met its initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1138 polypeptide is expressed at least two-fold higher in esophageal and kidney tumors as compared to normal esophageal and kidney tissue, respectively;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* an increase, generally leads to a corresponding change in the level of the encoded protein, *e.g.* an increase;

3. Given the differential expression of the PRO1138 mRNA in esophageal and kidney tumors compared to their normal tissue counterparts, it is more likely than not that the PRO1138 polypeptide is also differentially expressed in esophageal and kidney tumors compared to their normal tissue counterparts, making the claimed polypeptides useful as diagnostic tools, alone or in combination with other diagnostic tools.

Applicants understand the PTO to be making essentially two arguments in response to Applicants' asserted utility:

1. The PTO has argued that further details regarding Example 18 are required;

2. The PTO continues to rely on Pennica *et al.*, Hu *et al.*, Haynes *et al.*, Konopoka *et al.*, Lewin (Genes VI), Gokman-Polar *et al.* as well as newly cited references by Chen *et al.* (Mol. and Cell. Proteomics, (2002) 1:304-313), Gygi *et al.* (Mol. and Cell. Bio., (1999) 19(3):1720-30), and Anderson and Seilhamer (Electrophoresis 1997; 18:533-37) to support its assertion that gene amplification is not correlated with mRNA levels, and mRNA levels are not correlated with

polypeptide levels. Therefore, the specification "provides a mere invitation to experiment for establishing a specific and substantial use for the claimed polypeptides, which does not reasonably extrapolate to a readily available utility." *Office Action* at 17.

Applicants respectfully submit that in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

The Data Reporting Differential Expression of PRO1138 mRNA is Sufficient to Provide Utility for the mRNA as a Diagnostic Tool

Applicants submit that the PTO's position that additional details regarding Example 18 – such as the number of samples tested, the numerical values of expression, or whether the results are statistically significant – are required to establish utility for the claimed polypeptides is beyond that required under 35 U.S.C. §101. Applicants' statement of utility is presumed to be true, and further evidence to establish utility should not be required. *See In re Langer*, 503 F.2d at 1391, 183 USPQ at 297; *In re Malachowski*, 530 F.2d 1402, 1404, 189 USPQ 432, 435 (CCPA 1976); *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); *M.P.E.P.* §2107.02 (III). Requests for additional evidence should be imposed rarely, such as only when a statement is incredible in the light of the knowledge of the art, or factually misleading. *In re Citron*, 325 F.2d 248, 139 USPQ 516 (CCPA 1963); *M.P.E.P.* §2107.02 (V). In addition, as stated above, the standard for establishing a utility is a low one, and statistical certainty is not required:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

Notwithstanding the presumption of utility that should be accorded to Applicants' claimed polypeptides, Applicants previously submitted a copy of a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. As discussed previously, the declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue.

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," and that the samples were made from pooled samples of tumor and corresponding normal tissue, increasing the accuracy of the data, thus establishing their reliability. *See Grimaldi Declaration* at ¶¶ 5 and 7.

In addition, he explains that, contrary to the PTO's assertions, "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." *Grimaldi Declaration* at ¶7. Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant, as is the baseline level of expression. As Mr. Grimaldi states, "[i]f a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor." *Id.*

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." *PTO Utility Examination Guidelines* (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the PTO's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996).

The PTO also relies on Hu *et al.* to indicate that the art would question the importance of differential expression of a gene that is less than 10-fold. In addition to the reasons articulated in Applicants' arguments of record, the PTO's reliance on Hu is also misplaced because Applicants are not relying on microarray data as discussed in Hu:

> In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study. *Hu* at 405, left column, first paragraph (emphasis added).

Instead, Applicants are relying on a more accurate and reliable method of assessing changes in mRNA level, namely quantitative PCR analysis. In a recent study by Kuo *et al.*, (Proteomics 5(4):894-906 (2005)), the authors used microarray analysis combined with proteomic analysis using two-dimensional gel electrophoresis to examine changes in gene expression in leukemia cell lines. The authors report that "[c]omparison of microarray and proteomic expression profiles showed poor correlation. Use of more reliable and sensitive analyses, such as reverse transcriptase polymerase chain reaction [RT-PCR], Western blotting and functional assays, on several genes and proteins, nonetheless, confirmed that there is indeed good correlation between mRNA and protein expression." *Kuo et al.* at Abstract (emphasis added) (attached as Exhibit 1). Thus, even if accurate, Hu's statements regarding microarray studies are not relevant to the instant application which does not rely on microarray data.

Finally, Applicants note that the Federal Circuit has clearly rejected a requirement that evidence of utility be numerically precise or statistically significant. In *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. 881 (C.C.P.A. 1980), the issue in the interference was whether Nelson had shown at least one utility for the compounds at issue to establish an actual reduction to practice. *Id.* at 855. The Appellants relied on two tests to prove practical utility: an *in vivo* rat blood pressure (BP) test and an *in vitro* gerbil colon smooth muscle stimulation (GC-SMS) test. In the BP test, responses were categorized as either a depressor (lowering) effect or a pressor (elevating) effect. *Id.* The Board held that Nelson had not shown adequate proof of practical utility, characterizing the tests as "rough screens, uncorrelated with actual utility." *Id.* at 856.

On appeal the C.C.P.A. reversed, holding that the Board "erred in not recognizing that tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use." *Id.* (emphasis added).

Bowler argued that the BP and GC-SMS tests were inconclusive showings of pharmacological activity since confirmation by statistically significant means did not occur until after the critical date. The Court rejected this argument, stating that "a rigorous correlation is not necessary where the test for pharmacological activity is reasonably indicative of the desired response." *Id.* (emphasis added). The Court concluded that a "reasonable correlation" between

the observed properties and the suggested use was sufficient to establish practical utility. *Id.* at 857 (emphasis added).

This case is of importance because the Court rejected the notion that the testing must be statistically significant to support a practical utility. *Nelson*, 626 F.2d at 857. Likewise, qualitative characterizations of a test compound as either increasing or decreasing blood pressure was acceptable. *Id.* at 855 (stating that responses were categorized as either a depressor (lowering) effect or a pressor (elevating) effect). This is the same as the data in Example 18 relied on by Applicants, where the change in mRNA levels is described as "more highly expressed." The PTO's requirement that Applicants provide numerical precision and statistical certainty to establish utility is simply wrong, and contrary to established standards for utility. Thus, these arguments do not support the PTO's position as they do not lead one skilled in the art to question Applicants' asserted utility.

In conclusion, Applicants submit that the evidence reported in Example 18, supported by the first Grimaldi Declaration, establishes that there is at least a two-fold difference in PRO1138 mRNA between esophageal and kidney tumors compared to their respective normal tissue counterparts. The PTO has not offered any evidence or arguments to the contrary, and therefore any challenge to the sufficiency of the data with respect to the utility of the nucleic acid is inappropriate. Therefore, the only issue which remains is whether the data in Example 18 regarding differential expression of the PRO1138 mRNA are reasonably correlated with differential expression of the PRO1138 polypeptide such that the antibodies to the PRO1138 polypeptide have utility as diagnostic tools as well. As discussed below, even if the PTO has established a reasonable doubt regarding Applicants' assertion that they are reasonably correlated, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level more often than not lead to corresponding changes in protein level.

The PTO's Evidence is Not Relevant to Determining Whether a Change in mRNA Level for a Particular Gene lead to Corresponding Change in the Level of the Encoded Protein

Applicants turn next to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein;

given Applicants' evidence of differential expression of the mRNA for the PRO1138 polypeptide in esophageal and kidney tumors, it is likely that the PRO1138 polypeptide is also differentially expressed; and proteins differentially expressed in certain tumors have utility as diagnostic tools.

In response to Applicants' assertion, the PTO relies on Pennica *et al.*, Hu *et al.*, Haynes *et al.*, Konopoka *et al.*, Lewin (Genes VI), Gokman-Polar *et al.* as well as newly cited references by Chen *et al.*, Gygi *et al.*, and Anderson and Seilhamer.

Applicants have previously discussed at length why the Pennica *et al.*, Hu *et al.*, Haynes *et al.*, Konopoka *et al.*, Lewin (Genes VI), Gokman-Polar *et al.* references are not relevant to the issue of whether changes in mRNA level for a particular gene lead to changes in protein level. Briefly stated, references such as Pennica and Konopka which the PTO cites to teach that gene copy number does not equate with mRNA number are not relevant because Applicant does not rely on any relationship between gene copy number and mRNA levels. Likewise, references such as Haynes, Gygi, Anderson, and portions of Chen which discuss the correlation between static levels of mRNA and static levels of protein across different genes are also not relevant – Applicants rely only on the assertion that changes in mRNA level generally lead to corresponding changes in the encoded protein level. Applicants incorporate by reference the previous arguments made regarding these issues, and will not repeat them here.

However, in an attempt to illustrate why references which relate to static global levels of mRNA and protein across different genes are not relevant to Applicants' asserted utility, Applicants offer the following illustration and analogy with the understanding that like all illustrations and analogies, they are not perfect and therefore do not represent any admissions or binding statements regarding Applicants' disclosure or invention.

Haynes, Gygi, Anderson, and portions of Chen all discuss whether there is a correlation between the static level of mRNAs and proteins globally, *i.e.* across different genes. This is equivalent to conducting a hypothetical Experiment 1, where a particular cell type has 100 copies of mRNA for gene X, 200 copies of mRNA for gene Y, and 400 copies of mRNA for gene Z. If there is a global correlation between static mRNA levels and protein levels across genes, the ratio of the amount of proteins X:Y:Z would be approximately 1:2:4. This is essentially what the cited references examined.

In contrast, Applicants are relying on a correlation between changes in mRNA level for a particular gene leading to a corresponding change in the level of the encoded protein. For example, in hypothetical Experiment 2, if gene X has 100 copies of mRNA per cell in condition A (*e.g.* normal), and 200 copies of mRNA for gene X in condition B (*e.g.* tumor), the ratio of the amount of protein X in condition A:B would be approximately 1:2, such that there is a correlation between the change in the level of mRNA and protein for a particular gene.

The PTO argues that because there is no correlation between static levels of mRNA and protein across genes, as illustrated by Experiment 1, one of skill in the art would not expect an increase or decrease in the amount of mRNA for a particular gene to result in a corresponding change in the amount of the encoded protein, as illustrated in Experiment 2. This is simply wrong.

For example, Haynes reports that the amount of protein produced by similar levels of mRNA varied by as much as fifty-fold, and that similar amounts of protein were sustained by amounts of mRNA that varied by as much as forty-fold. *Haynes* at 1863, first full paragraph. Based on these results, Haynes concludes that "protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript." *Id.*

This is analogous to a finding that on one gallon of gas, a hybrid car can travel 70 miles but a large truck can only travel 5 miles, or that to travel 70 miles, a hybrid car requires 1 gallon of gas, but a large truck requires 14 gallons. That is to say, there are many things which affect the fuel efficiency of a car. Based on these observations, one could conclude that given the lack of correlation between the amount of gas in an automobile and the distance it travels, one cannot predict how far an automobile will travel based on the amount of gas in the tank.

Even if true, Haynes' data and conclusions are irrelevant to Applicants' assertion, which is that increasing or decreasing the amount of mRNA for a particular gene will result in a corresponding increase or decrease in the amount of the encoded protein. This is analogous to increasing or decreasing the amount of gas in an automobile – it will travel farther if you add more gas, and not as far with less. The fact that there are many things which affect fuel efficiency and therefore you cannot predict how far an automobile will travel without knowing if it is a hybrid or a large truck is irrelevant – both a hybrid and a truck travel farther on more gas, and not as far on less.

Similarly, Chen *et al.* report that plotting the level of mRNA for a particular gene against the level of the corresponding protein as measured across numerous samples, they found a lack of correlation for most genes studied. *Chen* at Abstract. However, with the exception of three genes reported in Figures 2A-2C, Chen does not indicate whether the level of mRNA varied significantly across samples, and Chen did not select samples or genes which were expected to vary across samples (*e.g.* normal versus tumor). Therefore, it is not known if Chen examined changes in mRNA level, or if the level of mRNA was unchanged. Therefore, the relevance of Chen's finding to Applicants' asserted correlation between changes in mRNA and protein is not known.

By analogy, if a person drives a particular car as far as possible on 5 gallons of gas 20 different times, and then plots the amount of gas against the distance driven, a lack of correlation between the amount of gas and distance is meaningless, and merely reflects systematic error in measuring the amount of gas and distance driven. Only if substantially different amounts of gas were plotted against their respective distances can you answer the question of whether increasing or decreasing the amount of gas results in increasing or decreasing the distance driven.

Applicants emphasize, and the PTO will recognize, that these are simplified illustrations to demonstrate the difference between the two issues being examined. However, these illustrations make clear that even if there is no correlation in the first experiment looking at static levels of mRNA and protein across different genes, there can still be a correlation between changes in mRNA and protein for a particular gene as examined in the second experiment. As these illustrations make clear, the PTO's evidence simply is not relevant to answering the question of whether it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true.

Applicants' Evidence Establishes that a Change in mRNA Level for a Particular Gene lead to a Corresponding Change in the Level of the Encoded Protein

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, a copy of the declaration of Paul Polakis, Ph.D., excerpts from the Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell

(3rd ed. 1994) and (4th ed. 2002), excerpts from the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)), a reference by Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, and a reference by Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002). The details of the teachings of these declarations and references, and how they support Applicants' asserted utility, are of record and will not be repeated here.

Applicants submit herewith a copy of a second Declaration by Dr. Polakis (attached as Exhibit 2) that presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (i.e., greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' second Declaration says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the PTO to draw independent conclusions.

The case law has clearly established that in considering affidavit evidence, the PTO must consider all of the evidence of record anew. *See in re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976); *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996), *quoting In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner." *Id.* at 1583. Applicants also respectfully draw the PTO's attention to the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." *66 Fed. Reg. 1098, Part IIB (2001).*

In addition to the supporting references previously submitted by Applicants, Applicants submit the following references to further support the assertion that changes in mRNA levels generally lead to corresponding changes in the level of the encoded polypeptide.

In a comprehensive study by Orntoft *et al.* (Mol. Cell. Proteomics. 2002; 1(1):37-45) (previously submitted with IDS, attached hereto as Exhibit 3), the authors examined gene amplification, mRNA expression level, and protein expression in pairs of non-invasive and invasive human bladder tumors. *Id.* at Abstract. The authors examined 40 well resolved abundant known proteins, and found that "[i]n general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations. Only one gene showed disagreement between transcript alteration and protein alteration." *Id.* at 42, col. 2. The alternations in mRNA and protein included both increases and decreases. *Id.* at 43, Table II. Clearly, a correlation in 39 of 40 genes examined supports Applicants' assertion that changes in mRNA level generally lead to corresponding changes in protein level.

In a study by Wang *et al.* (Urol. Res. 2000; 28(5):308-15) (abstract attached as Exhibit 4) the authors report that down-regulation of E-cadherin protein has been shown in various human tumors. *Id.* at Abstract. In the reported study, the authors examined the expression of cadherins and associated catenins at the mRNA level in paired tumor and nonneoplastic primary prostate cultures. They report that "[s]ix of seven cases of neoplastic cultures showed moderately-to-markedly decreased levels of E-cadherin and P-cadherin mRNA. Similar losses of alpha-catenin and beta-catenin mRNA were also observed." *Id.* As Applicants' assertion would predict, the authors state that the mRNA measures showed "good correlation" with the results from protein measures. The authors conclude by stating that "this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied." *Id.*

In a more recent study by Munaut *et al.* (Int. J. Cancer. 2003; 106(6):848-55) (abstract attached as Exhibit 5) the authors report that vascular endothelial growth factor (VEGF) is expressed in 64-95% of glioblastomas (GBMs), and that VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial cells. *Id.* at Abstract. The authors explain that infiltrating tumor cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix

metalloproteinases (MMPs). In the present study, the authors "used quantitative RT-PCR, Western blot, gelatin zymography and immunohistochemistry to study the expression of VEGF, VEGFR-1, VEGFR-2, sVEGFR-1, neuropilin-1, MT1-MMP, MMP-2, MMP-9 and TIMP-2 in 20 human GBMs and 5 normal brains. The expression of these MMPs was markedly increased in most GBMs with excellent correlation between mRNA and protein levels." *Id.* Thus, the results support Applicants' assertion that changes in mRNA level lead to corresponding changes in protein level.

In another recent study, Hui *et al.* (Leuk. Lymphoma. 2003; 44(8):1385-94 (abstract attached as Exhibit 6) used real-time quantitative PCR and immunohistochemistry to evaluate cyclin D1 mRNA and protein expression levels in mantle cell lymphoma (MCL). *Id.* at Abstract. The authors report that seven of nine cases of possible MCL showed overexpression of cyclin D1 mRNA, while two cases showed no cyclin D1 mRNA increase. *Id.* Similarly, "[s]ix of the seven cyclin D1 mRNA overexpressing cases showed increased cyclin D1 protein on tissue array immunohistochemistry; one was technically suboptimal." *Id.* The authors conclude that the study "demonstrates good correlation and comparability between measure of cyclin D1 mRNA ... and cyclin D1 protein." *Id.* Thus, this reference supports Applicants' assertion.

In a recent study by Khal *et al.* (Int. J. Biochem. Cell Biol. 2005; 37(10):2196-206) (abstract attached as Exhibit 7) the authors report that atrophy of skeletal muscle is common in patients with cancer and results in increased morbidity and mortality. *Id.* at Abstract. To further understand the underlying mechanism, the authors studied the expression of the ubiquitin-proteasome pathway in cancer patient muscle using a competitive RT-PCR to measure expression of mRNA for proteasome subunits C2 and C5, while protein expression was determined by western blotting. "Overall, both C2 and C5 gene expression was increased by about three-fold in skeletal muscle of cachectic cancer patients (average weight loss 14.5+/-2.5%), compared with that in patients without weight loss, with or without cancer. ... There was a good correlation between expression of proteasome 20Salpha subunits, detected by western blotting, and C2 and C5 mRNA, showing that increased gene expression resulted in increased protein synthesis." These findings support Applicants' assertion that changes in mRNA level lead to changes in protein level.

Maruyama *et al.* (Am. J. Patho. 1999; 155(3):815-22) (abstract attached as Exhibit 8) investigated the expression of three Id proteins (Id-1, Id-2 and Id-3) in normal pancreas, in pancreatic cancer and in chronic pancreatitis (CP). The authors report that pancreatic cancer cell lines frequently coexpressed all three Ids, "exhibiting good correlation between Id mRNA and protein levels." *Id.* at Abstract. In addition, the authors teach that all three Id mRNA levels were expressed at high levels in pancreatic cancer samples compared to normal or CP samples. At the protein level, Id-1 and Id-2 staining was faint in normal tissue, while Id-3 ranged from weak to strong. In contrast, in the cancer tissues "many of the cancer cells exhibited abundant Id-1, Id-2, and Id-3 immunoreactivity," and Id-1 and Id-2 protein was increased significantly in the cancer cells by comparison to the respective controls, mirroring the overexpression at the mRNA level. Thus, the authors report that in both cell lines and tissue samples, increased mRNA levels leads to an increase in protein overexpression, supporting Applicants' assertion.

Support for Applicants' assertion is also found in an article by Caberlotto *et al.* (Neurosci. Lett. 1999; 256(3):191-4) (abstract attached as Exhibit 9). In a previous study, the authors investigated alterations of neuropeptide Y (NPY) mRNA expression in the Flinders Sensitive Line rats (FSL), an animal model of depression. *Id.* at Abstract. The authors reported that in the current study, that NPY-like immunoreactivity (NPY-LI) was decreased in the hippocampal CA region, and increased in the arcuate nucleus, and that fluoxetine treatment elevated NPY-LI in the arcuate and anterior cingulate cortex. The authors state that "[t]he results demonstrate a good correlation between NPY peptide and mRNA expression." Thus, increases and decreases in mRNA levels were reflected in corresponding changes in protein level.

Misrachi and Shemesh (Biol. Reprod. 1999; 61(3):776-84) (abstract attached as Exhibit 10) investigated their hypothesis that FSH regulates the bovine cervical prostaglandin E(2) (PGE(2)) synthesis that is known to be associated with cervical relaxation and opening at the time of estrus. *Id.* at Abstract. Cervical tissue from pre-estrous/estrous, luteal, and postovulatory cows were examined for the presence of bovine (b) FSH receptor (R) and its corresponding mRNA. The authors report that bFSHR mRNA in the cervix was maximal during pre-estrus/estrus, and that the level of FSHR protein was significantly higher in pre-estrous/estrous cervix than in other cervical tissues. *Id.* The authors state that "[t]here was a good correlation between the 75-kDa protein expression and its corresponding transcript of 2.55

kb throughout the estrous cycle as described by Northern blot analysis as well as RT-PCR." *Id.* Thus, changes in the level of mRNA for bFSHR led to corresponding changes in FSHR protein levels, a result which supports Applicants' assertion.

In a study by Stein *et al.* (J. Urol. 2000; 164(3 Pt 2):1026-30) (abstract attached as Exhibit 11), the authors studied the role of the regulation of calcium ion homeostasis in smooth muscle contractility. *Id.* at Abstract. The authors investigated the correlation between sarcoplasmic endoplasmic reticulum, calcium, magnesium, adenosine triphosphatase (SERCA) protein and gene expression, and the contractile properties in the same bladder. Partial bladder outlet obstructions were created in adult New Zealand white rabbits, which were divided into control, sham operated and obstructed groups. Stein *et al.* report that "[t]he relative intensities of signals for the Western [protein] and Northern [mRNA] blots demonstrated a strong correlation between protein and gene expression. ... The loss of SERCA protein expression is mediated by down-regulation in gene expression in the same bladder." *Id.* This report supports Applicants' assertion that changes in mRNA level, e.g. a decrease, lead to a corresponding change in the level of the encoded protein, e.g. a decrease.

In an article by Gou and Xie (Zhonghua Jie He He Hu Xi Za Zhi. 2002; 25(6):337-40) (abstract attached as Exhibit 12) the authors investigated the expression of macrophage migration inhibitory factor (MIF) in human acute respiratory distress syndrome(ARDS) by examining the expression of MIF mRNA and protein in lung tissue in ARDS and normal persons. *Id.* at Abstract. The authors report "undetectable or weak MIF mRNA and protein expression in normal lungs. In contrast, there was marked upregulation of MIF mRNA and protein expression in the ARDS lungs." *Id.* This is consistent with Applicants' assertion that a change in mRNA for a particular gene, e.g. an increase, generally leads to a corresponding change in the level of protein expression, e.g. an increase.

These studies are representative of numerous published studies which support Applicants' assertion that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Applicants submit herewith an addition 70 references (abstracts attached as Exhibit 13) which support Applicants' assertion.

In addition to these supporting references, Applicants also submit herewith additional references which offer indirect support of Applicants' asserted utility. As discussed in detail

above, Applicants have challenged the relevance of references such as Haynes *et al.*, Gygi *et al.*, Anderson *et al.*, and Chen *et al.* which do not attempt to examine the correlation between a change in mRNA level and a change in the level of the corresponding protein level. Because the PTO continues to rely on these references, Applicants are submitting references which report results that are contrary to the PTO's cited references and offer indirect support for Applicants' asserted utility.

For example, in an article by Futcher *et al.* (Mol. Cell Biol. 1999; 19(11):7357-68) (abstract attached as Exhibit 14) the authors conducted a study of mRNA and protein expression in yeast which was nearly identical to the one conducted by Gygi *et al.* and reported in Haynes *et al.* Contrary to the results of the earlier study by Gygi, Futcher *et al.* report "a good correlation between protein abundance, mRNA abundance, and codon bias." *Id.* at Abstract.

In a study which is more closely related to Applicants' asserted utility, Godbout *et al.* (J. Biol. Chem. 1998; 273(33)21161-8) (abstract attached as Exhibit 15) studied the DEAD box gene, DDX1, in retinoblastoma and neuroblastoma tumor cell lines. The authors report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." *Id.* Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Similarly, in an article by Papotti *et al.* (Virchows Arch. 2002; 440(5):461-75) (abstract attached as Exhibit 16) the authors examined the expression of three somatostatin receptors (SSTR) at the mRNA and protein level in forty-six tumors. *Id.* at Abstract. The authors report a "good correlation between RT-PCR [mRNA level] and IHC [protein level] data on SSTR types 2, 3, and 5." *Id.*

Van der Wilt *et al.* (Eur. J. Cancer. 2003; 39(5):691-7) (abstract attached as Exhibit 17) studied deoxycytidine kinase (dCK) in seven cell lines, sixteen acute myeloid leukemia samples, ten human liver samples, and eleven human liver metastases of colorectal cancer origin. *Id.* at Abstract. The authors report that "enzyme activity and protein expression levels of dCK in cell lines were closely related to the mRNA expression levels" and that there was a "good correlation between the different dCK measurements in malignant cells and tumors." *Id.*

Grenback *et al.* (Regul. Pept. 2004; 117(2):127-39) (abstract attached as Exhibit 18) studied the level of galanin in human pituitary adenomas using a specific radioimmunoassay. *Id.*

at Abstract. The authors report that "[i]n the tumors analyzed with in situ hybridization there was a good correlation between galanin peptide levels and galanin mRNA expression." *Id.*

Similarly, Shen *et al.* (Blood. 2004; 104(9):2936-9) (abstract attached as Exhibit 19) examined the level of B-cell lymphoma 2 (BCL2) protein expression in germinal center (GC) B-cells and diffuse large B-cell lymphoma (DLBCL). *Id.* at Abstract. The authors report that "GC cells had low expression commensurate with the low protein expression level" and that in DLBCL the level of BCL2 mRNA and protein expression showed "in general, a good correlation." *Id.*

Likewise, in an article by Fu *et al.* (Blood 2005; 106(13):4315-21) (abstract attached as Exhibit 20) the authors report that six mantle cell lymphomas studied "expressed either cyclin D2 (2 cases) or cyclin D3 (4 cases)." *Id.* at Abstract. "There was a good correlation between cyclin D protein expression and the corresponding mRNA expression levels by gene expression analysis." *Id.*

These examples are only a few of the many references Applicants could cite in rebuttal to the PTO's arguments. Applicants submit herewith 26 additional references (abstracts attached as Exhibit 21) which also support Applicants' assertion in that the references report a correlation between the level of mRNA and corresponding protein, contrary to the assertion of the PTO that mRNA and protein levels are not correlated.

In summary, Applicants submit herewith a total of 113 references in addition to the declarations and references already of record which support Applicants' asserted utility, either directly or indirectly. These references support the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions (*see, e.g.*, abstracts attached as Exhibit 22). However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a

person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

In conclusion, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1138 mRNA is differentially expressed in esophageal and kidney tumors compared to their normal tissue counterparts, the PRO1138 polypeptide will likewise be differentially expressed in esophageal and kidney tumors. This differential expression of the PRO1138 polypeptide makes the claimed polypeptides useful as diagnostic tools for cancer, particularly esophageal and kidney cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed polypeptides related to PRO1138. Applicants respectfully disagree.

Specific utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1138 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the gene for the PRO1138 polypeptide is expressed at least two-fold higher in esophageal and kidney tumors as compared to normal esophageal and kidney tissue, respectively. These data are strong evidence that the PRO1138 gene and polypeptide are associated with esophageal and kidney tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1138 gene and polypeptide with a specific disease. The asserted utility for the claimed polypeptides as diagnostic tools for cancer, particularly esophageal and kidney tumors, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Utility – Conclusion

Applicants remind the PTO that the evidence supporting utility does not need to be direct evidence, nor does it need to provide an exact correlation between the submitted evidence and the asserted utility. Instead, evidence which is "reasonably" correlated with the asserted utility is sufficient. *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996) ("a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (same); *Nelson v. Bowler*, 626 F.2d 853, 857, 206 U.S.P.Q. 881 (C.C.P.A. 1980) (same). In addition, utility need only be shown to be "more likely than not true," not to a statistical certainty. *M.P.E.P.* at § 2107.02, part VII (2004). Considering the evidence as a whole in light of the relevant standards for establishing utility, Applicants have established at least one specific, substantial, and credible utility. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO also maintains its rejection of pending Claims 6-17 under 35 U.S.C. § 112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. *Office Action* at 17-18.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. To the extent that the enablement rejection is based on a lack of utility, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

The PTO further rejects pending Claims 6 and 11-17 as failing to comply with the enablement requirement. The PTO asserts that a statement assuring the availability of material deposited in the ATCC™ is required in order to enable the claimed polypeptides. The PTO has stated that the Declaration previously submitted is insufficient to obviate this rejection because it is not signed by an attorney of record over his or her registration number.

Applicants provide herewith a statement containing the information requested by the Examiner.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO also rejects pending Claims 6 and 12-17 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. Specifically, the PTO alleges that the specification does not provide sufficient distinguishing identifying characteristics of the genus of claimed polypeptides.

The PTO has Failed to Meet Its Initial Burden of Rebutting the Presumption that the Pending Claims are Adequately Described

To overcome the presumption that the claimed subject matter is adequately described, the PTO must present "evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 U.S.P.Q. at 97." *M.P.E.P.* § 2163.04. During the course of prosecution, the PTO has made essentially two arguments in an attempt to rebut this presumption.

First, the PTO states that "[t]he specification contemplates that the polypeptides can be a homolog in other species or human variants as isolated from nature. This specification fails to teach any variation of SEQ ID NO:46 or fragment that complies with either of those contemplated situations." *Office Action* at 18.

Second, the PTO argues that the instant claims are not like Example 14 of the Written Description Guidelines, stating that:

> The disclosure of a single polypeptide with a single characteristic does not warrant genus claims. Applicants were not in possession of a genus. Applicants neither isolated, cloned or otherwise identified variants that fell within the genus.... There are no other disclosed nucleic acids or polypeptides that fall within the genus and meet that claimed characteristic of encoded by a polynucleotide that is more highly expressed or the isolated polypeptide or polypeptide more highly expressed in the recited tissue samples....The instant activity is distinguished from Example 14, because the claimed activity is not catalytic and the neither the specification nor the art provides for a correlation of structure with the claimed functions. The language of "more highly expressed" is a characteristic of the polypeptide.... The functions as disclosed in the Written Description guidelines are not mere characteristics (i.e. pI, molecular weight, glycosylation or not, more

> highly expressed) of the polypeptide. The specification does not provide a correlation of the structure with any function of a polypeptide. The art does not provide a correlation of the structure with the claimed function. The written description of the specification does not provide any such structural-functional correlation. *Office Action* at 19 (emphasis added).

The PTO has failed to meet its initial burden of rebutting the presumption that the written description is adequate because nowhere in any Office Action does the PTO specifically address Claims 14-17, or explain how its arguments apply to pending Claims 6 and 12-13 which are not directed to variant polypeptides. Instead, the PTO's arguments address only Claims 4-5.

The Current Invention is Adequately Described

As mentioned above, pending Claims 6 and 12-13 do not recite percent sequence identity, and therefore are adequately described by the disclosure of Figure 46, SEQ ID NO:46 and ATCC Deposit No. 209956.

Pending Claims 14-17 are directed to isolated polypeptides having at least 95% amino acid sequence identity to polypeptides related to disclosed SEQ ID NO:46 which satisfy the limitation "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:46 in esophageal or kidney tissue samples."

Contrary to the PTO's assertions which are directed only to canceled Claims 4-5, pending Claims 14-17 are analogous to the claims discussed in Example 14 of the written description training materials available on the PTO's website. In Example 14, the written description requirement was found to be satisfied for claims directed to polypeptides with 95% homology to a disclosed sequence that also possess a recited catalytic activity, where procedures for making variant proteins were routine in the art and the specification provided an assay for detecting the recited catalytic activity of the protein. This disclosure satisfies the written description requirement even though the applicant had disclosed only a single species and had not made any variants. The Guidelines state that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least

95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity." (emphasis added).

Like Example 14, Claims 14-17 have very high sequence homology to the disclosed sequence and must share an epitope sufficient to generate antibodies which specifically detect the polypeptide of SEQ ID NO:46 in esophageal or kidney tissue samples. As in Example 14, at the time of the effective filing date of the instant application, it was well known in the art how to make polypeptides with at least 95% amino acid sequence identity to the disclosed sequences. *See, e.g., Specification* at ¶¶ [0256]-[0271]. In addition, the specification discloses in detail how to make antibodies which specifically detect a particular PRO polypeptide, and how to use them to detect the PRO polypeptide in a particular tissue. *See, e.g., Specification* ¶¶ [0363]-[0379], [0407], and [0493]-[0499]; *see also Sutcliffe et al.,* Science (1983) 219:660-666 at 661-662 (teaching that "by following simple rules, one can in general select peptides that will elicit antibodies reactive with intact proteins") (attached as Exhibit 23). Like a particular catalytic activity, the function of being useful to produce an antibody specific to SEQ ID NO:46 is directly related to the structure of the claimed polypeptides. Thus, like Example 14, the genus of polypeptides that have at least 95% amino acid sequence identity to the disclosed sequences and possess the described functional activity are adequately described.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO:46, by specifying a high level of amino acid sequence identity, and by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejections under 35 U.S.C. § 112, second paragraph – Indefiniteness

The PTO has apparently rejected Claims 14-17 under 35 U.S.C. § 112, second paragraph, as being indefinite for the reasons of record, although it is not clear as the PTO also states that

the rejection is "withdrawn." *See Office Action* at 22. The PTO previously objected to the recitation of an "extracellular domain" and "the extracellular domain...lacking its associated signal sequence" because a signal sequence is not generally considered part of an extracellular domain.

Applicants note that Claims 14-17 as amended do not recite "an extracellular domain," or "the extracellular domain...lacking its associated signal sequence." Therefore Applicants request that the PTO withdraw the indefiniteness rejection of Claims 14-17 under 35 U.S.C. §112, second paragraph.

Claims 4-6, 8 and 12-17 are newly rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner states that "the claims are *prima facie* indefinite because the claims no longer define the metes and bounds of the signal peptide, such that the skilled artisan would be able to ascertain structure of the claimed polypeptides." Office Action at 22.

Legal Standard for Indefiniteness

The test for definiteness under 35 U.S.C. §112, second paragraph, is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986). If one skilled in the art is able to ascertain the meaning of claim terms in light of the specification, 35 U.S.C. §112, second paragraph, is satisfied. *M.P.E.P.* § 2173.02. "The requirement to 'distinctly' claim means that the claim must have a meaning discernible to one of ordinary skill in the art when construed according to correct principles....Only when a claim remains insolubly ambiguous without a discernible meaning after all reasonable attempts at construction must a court declare it indefinite." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1366, 71 USPQ2d 1081, 1089 (Fed. Cir. 2004).

The Claims are Definite

Claims 6, 8, 10 and 14-15 recite the phrase "associated signal peptide." At ¶ [0072] of the specification, it states that "Figure 46 shows the amino acid sequence (SEQ ID NO:46) derived from the coding sequence of SEQ ID NO:45 shown in Figure 45." Therefore, one of

skill in the art would recognize that Figure 46 shows the entire amino acid sequence for SEQ ID NO: 46. One of skill in the art would also recognize that Figure 46 identifies particular portions of SEQ ID NO: 46, including the signal peptide sequence. Because the "signal peptide" of SEQ ID NO:46 is taught in the specification, one skilled in the art is able to ascertain the meaning of this term as recited in the claims. Accordingly 35 U.S.C. §112, second paragraph, is satisfied, and the rejection of pending Claims 6, 8 and 12-17 as indefinite should be withdrawn.

Rejection Under 35 U.S.C. §102(b)

Pending Claims 6-7, 9, 11 and 14-15 are rejected under 35 U.S.C. § 102(b) as anticipated by STREMBL_25 database accession number Q9NY23, created October 1, 2000. The PTO asserts that the reference teaches a polypeptide sequence that has 100% sequence identity to SEQ ID NO:46. Applicants respectfully traverse.

To be anticipated under 35 U.S.C. §102(b), the invention must be patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States. Applicants submit that Q9NY23 is not prior art under 35 U.S.C. §102(b) because it was not published one year before the priority date for the claimed polypeptides. The instant application is a continuation of, and claims priority under 35 U.S.C. §120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. §120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. §120 to, US Application 09/380137 filed 8/25/1999, which is the National Stage filed under 35 U.S.C. §371 of PCT Application PCT/US99/12252 filed 6/2/1999, which claims priority under 35 U.S.C. §119 to US Provisional Application 60/088863 filed 6/11/1998. Applicants submit that for the reasons stated above, the claimed polypeptides have a credible, substantial, and specific utility. The sequences of SEQ ID NOs:45 and 46 were first disclosed in US Provisional Application 60/088863 filed 6/11/1998 in Figures 1 and 2. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed polypeptides, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35.

According to the PTO, Q9NY23 was created October 1, 2000. Thus, Q9NY23 was not published at least one year earlier than the August 24, 2000 filing date of Application PCT/US00/23328, or the June 11, 1998 filing date of US Provisional Application 60/088863. The instant application is entitled to priority to both, and therefore Q9NY23 cannot be cited as prior art against the instant application under 35 U.S.C. §102(b). Applicants therefore request that the PTO reconsider and withdraw the rejection of the Claims under 35 U.S.C. § 102(b).

Rejection Under 35 U.S.C. §102(e)

Pending Claims 6-17 are rejected under 35. U.S.C. § 102(e) as anticipated by Starling *et al.*, WO 01/46260 with priority to U.S. Provisional Appl. 60/172,025, filed December 23, 1999, or Starling *et al.*, U.S. 2002/0123617, with priority to U.S. Provisional Appl. 60/170,025, filed December 23, 1999. The PTO states that the references disclose identical teachings. The PTO alleges that the WO document teaches a polypeptide SEQ ID NO:4 that has 100% sequence identity to SEQ ID NO:46.

Applicants previously submitted the Declaration of Audrey Goddard, Paul J. Godowski, Austin L. Gurney and William I. Wood under 37 C.F.R. §1.131, which establishes that the presently claimed invention antedates the priority date the PTO has asserted for Starling *et al.*, December 23, 1999. The Declaration of Goddard *et al.* establishes that the presently claimed subject matter was conceived prior to the priority date of December 23, 1999, and diligently reduced to practice thereafter. Thus, Applicants respectfully submit that the cited references are not available as prior art.

As set forth in 37 C.F.R. § 1.131, a patent applicant "may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based." The Declaration submitted in the present application demonstrates that the claimed subject matter, more particularly a polypeptide having the sequence of SEQ ID NO:46, variants thereof and antibodies to the same, was conceived by Applicants prior to December 23, 1999. Furthermore, as evidenced by the Declaration and accompanying exhibits, Applicants exhibited diligence in reducing the subject matter of the claims to practice by performing various assays to confirm the function of the

polypeptide. Therefore, the Starling reference is not available as prior art under 35 U.S.C. § 102(e).

The PTO responds by stating that "[t]he declaration is not persuasive because it lacks evidence of conception of the polypeptide and variants and fails to point to explicit written description for the claimed invention and its claimed embodiments in the earlier filed documents." *Office Action* at 23.

As the declaration states, the sequences of SEQ ID NOs: 45 and 46 were first disclosed in U.S. Provisional Application 60/088863, filed June 11, 1998, as SEQ ID NOs: 1 and 3, in Figures 1A-B and 2. Clearly, the polypeptide of SEQ ID NO:46 was conceived at least by the filing date of the provisional application as it is disclosed therein as SEQ ID NO:3. In addition, variants of SEQ ID NO:46 and the remainder of the invention as presently claimed was also clearly conceived at least by the filing date of the provisional application, as a reading of the entire provisional application makes clear. For example, the provisional application states "[i]n another aspect, the invention concerns an isolated PRO1138 polypeptide, comprising an amino acid sequence having ... at least about 95% sequence identity to the sequence of amino acid residues 1 or about 23 to 335, inclusive or Figure 2 (SEQ ID NO:3)." *Prov. Appl. No. 60/088863* at 4. The provisional application also states "[i]n another aspect, the invention concerns a PRO1138 extracellular domain comprising an amino acid sequence having ... at least about 95% sequence identity to the sequence of amino acid residues 1 or about 23 to X of Figure 2 (SEQ ID NO:3), wherein X is any one of amino acid residues 219 to 228 of Figure 2 (SEQ ID NO:3)." *Id.* Also disclosed are the manufacture of antibodies to PRO1138, and their use to detect PRO1138 expression in specific tissue types. *See, e.g. Id.* at 22, 26-3239-40. Thus, contrary to the PTO's assertion, the provisional application clearly demonstrates conception of the invention by at least June 11, 1998, which is prior to the earliest priority date of either Starling reference, December 23, 1999. Following conception, the evidence presented with Applicants' declaration demonstrates diligent reduction to practice as Applicants developed primers and probes to test for the differential expression of PRO1138.

Thus, Applicants' declaration establishes that Applicants conceived of the invention prior to the earliest filing of Starling, and diligently reduced it to practice thereafter. As a matter of law, the Starling reference is not available as prior art under 35 U.S.C. § 102(e) because it does

not meet the statutory requirement of 35 U.S.C. § 102(e) that the cited art be "filed by another in the United States **before the invention by the applicant for patent**." (emphasis added). As permitted by 37 C.F.R. § 1.131, a patent applicant "may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based" – Applicants have done just that.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102(e).

Rejections under 35 U.S.C. § 112, first paragraph – New Matter

The PTO rejects pending claims 6, 9, 10, 12 and 13 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, stating that the recitation that the extracellular domain is amino acids 23-223 of SEQ ID NO:46 constitutes new matter.

Applicants respectfully disagree that one of skill in the art would not recognize the extracellular domain based on the disclosure of Figure 46. However, this rejection is moot in light of Applicants amendment of the claims to delete recitation of the language "extracellular domain."

The pending claims which recite "the amino acid sequence of amino acids 23-223 of SEQ ID NO:46" are supported by the specification as filed. Figure 46 discloses that the signal peptide is amino acids 1-22, that the transmembrane domain is amino acids 224-250, thus, the fragment between the two is amino acids 23-223. Paragraph [0017] of the specification states that polypeptides with the transmembrane domain deleted are contemplated, and several paragraphs state that "any other specifically defined fragment" of the PRO polypeptides is contemplated, including "an amino acid sequence lacking the signal peptide as disclosed herein." *See, e.g.,* ¶ [0014]. Thus, one of the fragments contemplated in the specification is the fragment that remains when the transmembrane domain and signal peptide are deleted – that is to say, the fragment between the signal peptide and the transmembrane domain of SEQ ID NO:46, amino acids 23-223.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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